

# THE BIOLOGICAL TREATMENT OF CANCER<sup>1</sup>

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## ANTIPARASITIC METHODS

It is the purpose of this paper to review critically some of the methods and results of the past two decades in cancer research, a branch of pathology which has not failed to share in the general progress of medicine. During this period innumerable experiments have been performed, and the most diverse materials employed, in an endeavor to solve the problem of the cure of cancer.

Thus Bra has employed cultures of *Nectria ditissima*, a parasitic myxomycete occurring in certain plants, and causing a disease resembling cancer in man. Cultures heated to 120° and filtered cause a febrile reaction in cancerous patients which is not found in healthy persons.

Mongour and Gentes, employing this method, found that while the pain, the hemorrhage, and the discharge ceased, cure did not take place, and a similar result has been recorded by Parlavecchio.

Bra later prepared an anticancerous vaccine from a parasite similar to that of plants, but obtained from human tumors. This vaccine, according to Silva and Vidal, caused a febrile reaction but no cures.

Schmidt stated that *Mucor racemosus* is the causative agent of cancer, and that preparations of its cultures exert a therapeutic effect in cancer patients. He published the statement that he

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The author has not read the proof.

had succeeded in increasing its virulence in rats to such a point that in successive inoculations up to the eighth generation he finally achieved 100 per cent of results in 8 rats, although in the first 40 animals tumors had developed in but 2 cases. Furthermore, treatment with dead cultures from tumors obtained in this way gave 20 to 25 per cent of cures.

In view of the negative results of Schuberg, Baisch, and von Dungern and Werner, these experiments may be regarded as quite without value.

Nevertheless, Schmidt and others have reported clinical cases of neoplasm cured by means of cancrin or antimeristem; thus Claes recorded a recurring sarcoma of the maxilla, Neander a neoplastic stenosis of the rectum, Aronsohn a cancer of the larynx, and Jenssen a cancrinoid of the tongue. But a study of these cases gives rise to some doubt regarding their nature. For example, Aronsohn's patient was a syphilitic with multiple laryngeal nodules, in whom the diagnostic reaction of Schmidt was negative. In Jenssen's case, again, the patient had an ulcer of the tongue in which the *Treponema pallidum* was easily demonstrable; cure resulted only after six months and a half of treatment, and was followed by abscess formation and subsequent scarring (gumma?).

Furthermore, Schmidt's conclusions have been severely criticized by Dreesmann on the basis of observations which he considered of positive value, and by Shaw-Mackenzie. Glenton Myler, also, in 9 cases seen in the Middlesex Hospital, noted the absence of any diagnostic reaction and of any therapeutic effect.

Beresnegowsky, in 7 cases of inoperable carcinoma at the Heidelberg Clinic, had nothing but negative results, while Winkler observed no effect on the tumors and called attention to the serious disturbances produced by the injections.

Beresnegowsky reported 2 patients who died without having been benefited and were examined histologically at biopsy and autopsy under Orth's direction. From these cases, one a recurrent gelatinous carcinoma of the breast, the other an infiltrating cancer of the larynx and epiglottis, Beresnegowsky concluded that neither from the clinical history, the autopsy, nor the mi-

croscopical examination, could any influence on the tumor be admitted, for the growth was not modified, metastases were not prevented, and the structure was not altered; the only definite result, he added, was the production in the first case of large multiple subcutaneous abscesses.

Czerny, wishing to reinforce the action of radium, tried out the combined action of serum and toxin. For this purpose the carcino of Schmidt was tested on 45 patients, 14 of whom carried out the complete treatment, while others continued it only for a time or refused to go on with it because the first injection caused inflammation and fever. Czerny pointed out that in cachectic patients with visceral metastases in important organs the treatment should not be attempted, and concluded that although in some cases there might have been seen a temporary modification of the disease, cure was not brought about in any. Similar reports have been made lately by Werner, Sick, Kolb, Bagge, Nordt, and Stockmann; in no case of genuine neoplasia has antimeristem shown any elective action worthy of note.

Wlaeff, an adherent of the theory of the blastomycetic origin of tumors, prepared a specific serum and immunized animals against blastomycetes obtained by culture from human tumors; and having noted that the serum protected rats and monkeys from blastomycetic infection, he tried it in human beings. Serum obtained from pigeons, chickens, geese, or donkeys and administered subcutaneously every five to eight days in doses of from 7 to 12 cm. to patients without metastases, was said to produce an improvement in the general condition, a reduction in the volume of the tumor, and an arrest of its development. Permanent cure did not take place, however, the neoplasms later resuming their growth.

Biondi, in a discussion of the serotherapy of tumors presented before the Italian Surgical Society in 1895, stated that the serum of animals immunized with the blastomycete of Sanfelice was without any influence on either sarcomas or epitheliomas, while Lucas-Championniere, Le Dentu, and Berger obtained only transitory arrest with Wlaeff's serum.

The significance of blastomycetes as neoplastic agents has been denied also, and on the basis of accurate and extensive research, by Laederich and Duval, Franchetti, Stropeni, Cao, Tiberti, Donati, Alessandri and Zapelloni, Magnini, and finally by Galeotti, who was formerly inclined to ascribe etiological importance to them.

In regard to the therapeutic action of the serum prepared by Sanfelice and used by him in cases of lymphosarcoma and carcinoma of dogs, it must be objected that spontaneous regression of this type of lymphosarcoma has been reported by Sticker, Bashford, Beebe and Ewing, and Veratti, and that many observers are not willing to include the growth among the true tumors.

In three cases of cancer of the breast in dogs, which were treated with the serum, disappearance of the growth did not take place, but Sanfelice reported degenerative changes and a connective tissue reaction; this, however, Veratti and Vidal considered evidence of partial spontaneous regression.

Doyen has given the name *Micrococcus neoformans* to a parasite which he believes to be the cause of tumors. Intraperitoneal inoculation in white mice is said to have caused the formation of tumors about the liver and pancreas, and an inflammatory reaction of the lung with hyperplasia of the bronchial epithelium. And foci of melanosarcoma were said to have followed the intraperitoneal injection of an emulsion of a human pigmented tumor mixed with *Micrococcus neoformans*. In rats, inflammatory changes were observed in the large intestine, with changes in the glands, and Doyen described also a papillary carcinoma of the bladder, a cystic fibroma of the tube, epithelial growths of the lung accompanied by myxocartilaginous new growths, and several lipomas.

But the variety of type assumed by these growths, no less than the lack of precision with which they are described, suggests doubt as to the actual nature of the lesions encountered, and the suspicion is aroused that they were either chance findings or simple inflammatory reactions. The example considered by Doyen the most valuable only increases these doubts, for the

"melanotic sarcoma" above mentioned may be explained by mere phagocytic pigmentation of the reactive tissue at the site of the injection.

Doyen administered preparations of his bacillus for therapeutic purposes, also, but as the cases were treated at the same time by surgery, x-rays, radium, thermocoagulation, and heat otherwise applied, there was such an accumulation of therapeutic procedures that it is difficult to determine what part of the result can be attributed to the antineoplastic vaccination. The diagnoses were not confirmed microscopically, and even clinically were far from certain. Histological reports are generally absent, even in the cases that were subjected to operation, though they would have been of great interest in establishing the diagnosis and determining the changes referable to the treatment.

Furthermore, Hornus, in his inaugural dissertation on this subject, prepared under the guidance of Doyen, speaks only of delayed development, amelioration of the symptoms, improvement in the general conditions, and prolongation of life, producing no evidence that might lead one to accept the treatment as a cure. Nor did Berger, Monod, Nelaton, Kirmisson, and Delbet observe any improvement in 26 patients treated by Doyen, and followed for five months; unfavorable observations have been reported also by Vidal and Bender, Paine and Morgan, Pattison, Thomson, Musgrave, Woodman, van Ermengem, and Debaisieux.

Nobody, in short, has yet succeeded in obtaining reliable results from methods of treatment based upon a specific causative agent. These results, furthermore, have been no better than those obtained on the basis of a parasitic etiology acknowledged to be erroneous, as, for example, in the case of Adamkiewicz's hypothesis or of procedures based upon germs to which no pathogenic importance is attached, like the streptococcus of Fehleisen, or the *Bacillus prodigiosus* in the methods of Coley and Emmerich and Scholl.

## PASSIVE IMMUNIZATION WITH TUMORS

Another group of investigators, without trying to determine the identity of the specific agent concerned in neoplasia, has attempted to secure active or passive immunization with tumor, on the hypothesis that some virus is contained in its tissues or that the tumor cells themselves are a virus.

This group includes Richet and Hericourt, who in 1895 immunized animals with osteosarcoma; the tumor was finely triturated and filtered through gauze and the liquid so obtained was injected intravenously into donkeys, dogs, or horses. The serum of these animals, collected seven to twelve days later, was introduced subcutaneously in doses of 3 cc., either in the neighborhood of the tumor or at a distance from it. It was asserted that noteworthy improvement in the general condition set in, that the tumors diminished in size, hemorrhages were arrested, ulcerated surfaces became clean, and that partial cicatrization resulted, though without permanent benefit being obtained. After a very short period the tumors again began to grow and the general unfavorable condition progressed in spite of continuation of the treatment. This was further accompanied, moreover, by evidences of intolerance, among which vomiting, diarrhea, lumbar pain, skin eruptions, headache, and fever were notable. Similar findings have been reported by Boureau, Boinet, Brunner, Bosc, Ceci, Barlerin, Biondi, Pascale, De Gaetano, Salvati, and Parascandolo.

Various modifications of the serum treatment have been suggested, especially since the early researches of Metalnikoff, Ehrlich, and von Dungern on cytotoxins. These suggested a specificity of cytolytins, and gave rise to the hope that a cytolytin might be prepared which would attack only tumor cells. The attempts begun by Richet and Hericourt were therefore continued by other investigators, among whom were Poncet and Dor, Charcot, Jensen, von Leyden and Blumenthal, Hoyten, Borrel, Lomer, Loeffler, Vidal, etc.

Dor, in 1900, injected a goat with a melanotic tumor and introduced the serum so obtained into two persons suffering

from melanosarcoma. After a period of subjective and objective improvement the first patient was lost sight of, while in the second case the treatment was interrupted by lack of serum.

Leyden and Blumenthal treated goats and sheep with epithelium from the breast, liver, or uterus, and injected the serum into persons suffering from epithelial new growths of the corresponding organs, but except for temporary improvement and transitory changes in the consistency and volume of the primary tumor and its metastases, no action was discernible.

Hoyten injected fluids from human carcinoma into dogs and inoculated their serum into patients; the results were more evident in the metastases than in the original tumor.

Lomer reported a case of recurrence in the scar of an operation for carcinoma of the breast. Half of this nodule was used for histological diagnosis, and the remainder disappeared following a series of injections of animal serum obtained after treatment with human epithelium. In the same way an axillary metastasis that appeared later was caused to retrogress.

Vidal has recently affirmed that it is possible to obtain a serum of considerable efficacy by injecting animals with human tumor of the same type as that which is to be treated. For this purpose he carried out the method of Besredka for antibacterial serums, injecting a fresh emulsion of tumor cells sensitized with the corresponding serum previously obtained. Furthermore, during the treatment of the animal from which the serum was to be obtained, he injected substances capable of bringing about a hyperleucocytosis in order to increase the antibody content. Curative sera thus prepared, which should possess specific properties and particularly that of cytolysis for the tumor cells, require a long period of administration because their action is slow. During this time, according to Vidal, the body of the patient reacts by the production of neutralizing substances forming an immune antiserum. To avoid this drawback, he prepared another serum from dogs treated with neutralizing blood from patients who for some time had been subjected to the immune serum, or with pleural or peritoneal effusion fluid from the same patients; in this way he obtained an anti-immune serum, or

serum N. After prolonged injections of an immune serum and of this serum N, Vidal obtained in some patients complete regression of their tumors.

But in spite of the various modifications suggested by Richet and Hericourt, serotherapy has not fulfilled expectations, and has even lost a great part of its experimental basis. Thus Jensen, who was among the first to carry out attempts at specific serotherapy in animals, has acknowledged that the regression observed by him in the transplanted tumors of mice that had been injected with serum from immunized rabbits, was spontaneous; that is, it often occurs without the use of any specific serum. This agrees with the experience of Bashford, Murray, and Cramer, who did not observe any effect from serotherapy when treated mice were compared with untreated controls.

Loeffler, who attempted to obtain an active serum from immunized donkeys, was obliged to admit that such a serum precipitated normal elements in the same degree as tumor cells.

In addition to a lack of specificity in the serum of immunized animals, and to its inefficacy, it is to be noted that the partial and temporary results referred to immune sera have also been described after the use of normal serum (Arloing and Courmont, and Augagneur).

#### ACTIVE IMMUNIZATION WITH TUMORS

Beside passive immunization, active immunization by vaccination with tumor has been attempted, in the hope of obtaining specific antibodies in the patient himself. Thus, Hoyten, in 1899, injected into the neoplasm tumor juices diluted with physiological salt solution, and reported favorable results.

von Leyden and Blumenthal spoke favorably of active immunization carried out according to their hypothesis. In the first notes published, it was stated that the expressed juices of new growths obtained from human beings at operation were tried on three patients. The tumors themselves did not undergo any important change, but indurated lymph-nodes in the neighborhood grew smaller and improvement was noted in the pain and



in the general condition; the nature of the lymphadenoid enlargement, however, was somewhat doubtful, since the neoplasms were ulcerated and therefore infected. Two of the cases are reported to have died.

Müller, trusting in the bactericidal action of glycerin, prepared his material by placing fresh tumor in 80 per cent glycerin; the mixture was kept for forty-eight hours at 37° and then diluted with physiological salt solution and injected in the mammary region. Seven cases were treated, six of which had carcinoma of the uterus and one an ovarian cyst undergoing carcinomatous change. The injections frequently produced abscesses and febrile symptoms, but no cure.

Other attempts at active immunization with tumor have been made without decisive results by Caan, Rovsing, Odier, Delbet, Graff, and Ranzi. Delbet, for example, injected into patients after radical operation the entire tumor reduced to a pulp; this material, without the addition of any bactericidal substance, was suspended in a small amount of physiological salt solution and introduced subcutaneously in two, three, or four different regions, according to its volume. It must be mentioned, however, that he preceded the operation and injection by a course of radiotherapy and the copious painting of raw surfaces with tincture of iodine, and followed it by the application of at least 3 cgm. of radium bromide between the sutured surfaces. This was allowed to remain in position for twenty-four hours, and ten days later *x*-ray treatment was again instituted. Only a short time was necessary to show that the method produced implanted tumors, a consequence which supervened in the cases of von Graff and Ranzi also.

Coca and Gilman have also taken up the matter of active immunization, inspired by the researches of Metalnikoff, von Dungern, and Hirschfeld. The patient's tumor was reduced to small fragments with scissors immediately after removal, repeatedly subjected to pressure, suspended in physiological salt solution, centrifuged, decanted, and finally treated with 0.5 per cent of phenol or toluol. The injections were generally carried out about six hours after the addition of the phenol, though

sometimes earlier when the extract was uncontaminated. The dose of the tissue for each treatment varied from 10 to 25 grams, the fluid being introduced into the abdominal wall through four to six different punctures. The inoculation often gave rise to a local reaction, but in no case did sufficient time elapse to enable one to come to a decision regarding the value of the method; in most cases there was a period of only a few days or months between the operation and the report. Furthermore, microscopical examinations and clinical reports are lacking.

The dangers inherent in active immunization when it is carried out by methods above mentioned have been clearly indicated by Wolff and Blumenthal. Wolff makes the following comment: "Autovaccination, as we have so far come to know it, always involves the danger that living cancer cells (or if one upholds the parasitic theory as von Leyden and others do, living parasites) may be introduced, to give rise later to the formation of new tumors."

#### HISTOGENETIC CHEMOTHERAPY

While stress had been laid on the principles of active immunization as recently as 1910 with the technic and the results just recounted, I had undertaken comparative observations on embryonal and tumor implantation as well as on the action of histogenic autolysates some years previously, and had treated tumors in animals and in man with fetal tissue or with tumor cells. My research and that of my collaborators was founded on the hypothesis of oncogenic disequilibrium, which would refer the origin of tumors to a state of disharmony, a disturbance of the factors regulating proliferation, during which they pass from under the control of the enzymes, hormones, and histolytic products which ordinarily guide them.

*Histotherapy on a biochemical basis, or histogenetic chemotherapy*, attempts to cure oncogenic disturbances and their effects by stimulating oncolysis. It is naturally limited by its own nature, as it is not possible to suppress all the abnormal functional activities to which the origin of tumors is due, nor is it possible to exceed the limited dose that can be injected.

The earliest experiments were carried out with autolysates and filtrates; the clinical course of transplanted tumors in relation to the host, spontaneous involution, and acquired resistance were also investigated, and the conclusion was finally reached that resistance depends on the absorption of histogenic substances and on the reaction produced by these. Later I undertook an investigation of the regression provoked by histogenic substances, either embryonal or neoplastic, and was able to establish a parallel between autolysis in vivo, by immunization, and autolysis in vitro by the method of histogenic therapeutics. The treatment was applied also to 36 patients with inoperable malignant growths, with a result which was summed up in 1910 as follows:

Objectively there may be an arrest or even a disappearance of the tumor, and anatomical changes may be observed which are sometimes definite enough to permit the assumption of local cure at least. Thus in favorable cases there may be observed a cytolysis of the tumor cells, gradually increasing until these have entirely disappeared; an intense small cell infiltration which is more pronounced about the blood-vessels; the appearance of numerous microphages, macrophages, and plasma cells; active connective tissue and vascular infiltration invading all portions, together with some giant cells; replacement by dense connective tissue; in short, the cessation of all phenomena associated with infiltration and growth. The tumor becomes soft and fluctuating, and aspiration in these cases reveals a clear fluid containing whitish flakes in suspension and having the character of a transudate. All these changes are perfectly comparable to those which I have already described in rat sarcomas treated by means of autolysates, and may be compared, also, to those characteristic of sarcomas or carcinomas which have been transplanted into rats immunized with embryonal tissues. They are similar, too, to those seen in receding tumors and in grafts of embryonal tissue in the second period of their cycle; that is, in the phase of regression and disappearance. It is a question, therefore, of physiopathological phenomena which can be explained according to general laws and which go on with greater intensity in accordance with the combined action of various factors.

The value of histogenic chemotherapy was promptly confirmed by numerous other investigators, and autolysates or

extracts have since then been generally used; by some authors in the way just described, by others through vaccination, which, under these conditions, does not involve the risk of implanted tumors which is present when emulsions are used.

For example, Abderhalden and Kohlhardt have referred explicitly to these researches in their experimental and clinical observations. They attempted to utilize only the antiblastic reaction obtained according to the technic and principles of protective ferments, which they were among the first to study intensively and which have been accepted by many others, at least so far as the specificity of tissues and lytic ferments is concerned.

Blumenthal desired to see the discussion limited to neoplastic tissue, since he denies that the same therapeutic or immunizing results can be obtained with normal tissue as with homologous tumor. But to deny the presence of resistance after treatment with normal tissue is to do away with the researches of Bashford, Schöne, Michaelis, Borrel and Bridé, Lewin, Apolant, Moreschi, Da Fano, Levin, Brancati, Magnini, Biach and Weltmann, Higuchi, Woglom, Loeb and Fleisher, Krongold, Jowleff, and Roffo; yet these have definitely proved the existence of immunity following treatment with skin, embryo emulsion, blood, mammary gland, liver, spleen, and thyroid. To deny this refractory state is, in fact, to deny some of the most important findings in the entire field of cancer research, and, leaving aside the various ideas concerning specificity, would mean abolishing the basis on which vaccination is founded, firmly established as this is by the tuberculin reaction and the resistance to transplanted tumors caused by absorption of injected tissues.

Recent observations, carried out especially in Italy, suggest an easy explanation of the curative mechanism of tissues in general. These have included the investigation of cancerous organs; of inoculation of tumor grafts into various organs; of the immunizing and therapeutic power of extracts from normal and pathological organs; of the effect upon receptivity or resistance of the removal of different organs; of differences between

normal and immune animals; and of the oncolytic variations in the serum of normal or tumor-bearing animals. Among the Italian investigators who have worked on these subjects are the following; Fichera, Ricci, Perez, Gussio, Almagia, Brancati, Magnini, Cimatori, Caravani, Mazza, Piantoni, Donati D'Agata, Serafini; the list of those in other countries includes von Graff, Apolant, Korentschwesky, Sweet, Saxon, Hilario, Loeb, and Freund and Kaminer.

The results of their observations lead to the conclusion that certain organs possessing active oncolytic and hyperplastic properties in normal or immune animals, are inactive in advanced life or in the presence of a large tumor; and furthermore, that the histogenic substances which have been found efficacious act both directly and indirectly.

The *direct* method depends on cytolytic ferments contained in the various tissues and organs (the isoferments of neoplastic autolyzed tissues, and the heteroferments of normal tissues or those undergoing active histolysis). The *indirect* is represented by stimulation of the organs producing oncolytic substances; under favorable conditions this can be effected by the constituents of various tissues.

These observations and conceptions are important, enabling one to understand, for example, the varying efficacy of the different tissues in proportion to their original content of oncolytic substances and the different degrees of antiblastic reaction which they can produce.

The observation by Bertrand, Daels and Deleuze, Sellei, Lunckenbein, and Schubert, that unsuitable dosage may cause an increase in the growth of a tumor instead of regression, was demonstrated some time since by me; and Gussio, Brancati, and Caravani hold similar views. This unfavorable action of large doses explains the negative results obtained in man by Austoni and Carraro, while, in considering the work of Uffreduzzi and Morpurgo on rats and mice, one must remember that chloroform rapidly inhibits the therapeutic action of autolysates, as has been shown by Levin, Lewin, Bauer, Latzel, and Wessely. Again, degenerative changes may be followed by

extension of the growth, with liberation of autolytic products and the institution of a negative phase marked by increasing failure of the oncolytic system and a hastening of the clinical course. The same condition follows intense radiation or the administration of large amounts of colloidal substances; these, instead of stimulating, seriously injure the inhibitory organs and bring about those unfavorable effects described by some writers. There is a connection between the methods just spoken of and the stimulation of chemotherapy. Indeed the direct action of the best known physical and chemical agents is accompanied by a no less important indirect effect recently illustrated by my experimental results, as well as by those of Brancati, Gussio, Caravani, and others, among whom Fränkel and Kimball should be mentioned especially; these have demonstrated an increased resistance in healthy animals suitably radiated before inoculation.

Indirect action deserves the more interest in that there is less definitely a specific factor concerned, the condition reducing itself to a greater sensibility of the neoplastic elements. Their susceptibility subjects them to the general laws of Guilleminot, according to which cells are the more sensitive to radiation the greater their karyokinetic activity, and, therefore, the shorter their vital cycle.

On the other hand, it is noteworthy that doses of radioactive substances only a little greater than those employed, and usually insufficient to cause the disappearance of tumors, are frequently responsible for serious lesions of the body tissues, which, according to the intensity and frequency of the radiation, may pass from hyperplasia to necrosis (Fränkel and Budde, Miller, Heinecke, Unseitig, and Steinhaus).

Thus, radioactive substances exert no specific action on the tumor cell, an impression that has been once again confirmed by Pentimalli. The truth of this statement is evident from the limited destruction of tumor and the extensive damage to healthy tissues produced by strong and penetrating doses. The satisfactory results hoped for through the employment of large amounts have not, therefore, been gained, as not only clinical

observation, but the histological investigations of Aschoff, Steinhaus, Versè, Simon, and Dürck only too clearly demonstrate.

The same may be said of the various chemical substances that have been suggested. For example, the metals which have been reported on by von Wassermann in animals and by Quarelli in man, do not show any specific deposition in the tumor, when normal and pathological tissues from the same organ are compared by extraction, or by polarimetric and histochemical methods. The result is rather that the liver and spleen are generally found to be richest in the substances used. When the quantities introduced are excessive, there are found intense hyperemia, hemorrhage, and degeneration in many organs; especially is this true of the hematopoietic system, as a consequence of which there occur changes in the blood picture (Robin, Ashard, Bardet, Girard, Dugern, de Ario).

On the whole, then, it may be said that the tumor cell has so far offered no specific point for attack by radioactive substances or by chemical agents. Yet in the organs of animals exposed to these measures, structural and functional conditions are encountered which throw some light upon the indirect action of the agents in question.

Thus when too active radiation is employed, or too large amounts of metals, autolysates, or extracts, there are found degenerative lesions and hemorrhages into the parenchyma of the more important organs, and into the tumor itself; and the neoplasm may even be stimulated to increased growth. But when the same measures are applied in suitable doses, a functional hyperplasia supervenes in the various organs, and especially in those appertaining to the hematopoietic system (Fichera, Brancati, Gussio, Caravani, and Szecsi), which is accompanied by arrested development in the tumor or even by its complete disappearance.

Again, in both animals and man, the *x*-rays or radium in suitable amounts may bring about leucopenia quickly alternating with leucocytosis. In this way one may cause succeeding cycles of leucolysis and abundant regeneration, as has been especially shown by Aubertin, Beaujard, Guilleminot, Manouk-

hine, Murphy, Morton, and Nurenberg. Similar results have been obtained by the injection of colloidal substances which have been found capable of producing effects on the blood-forming organs by von Hansemann, de Laire, de Ario, Szeesi, and Pentimalli. That the same thing happens after the use of histogenic autolysates is shown by the general condition and by the state of the blood, according to my observations and those of Almagia, Vaughan, and H. Ross.

Under these conditions one may find an augmentation in the size of the liver and spleen, as well as an increase in the function of the blood-forming organs; the latter involves not only the bone-marrow and spleen, but also the liver, even in animals that are no longer very young. These changes, on the other hand, belong especially to the first years of life, that is, to a period in which spontaneous tumors are seldom seen, and are also observed in immune rats, so that they may be considered as an anatomical substratum of resistance (Fichera, Brancati, Goldmann, and Mazza).

The fact, therefore, that these visceral changes are found both in tumor-bearing animals and in normal ones treated by the various agents mentioned above, suggests the possibility of a participation of these functional activities in the regression of tumors.

If organs inhibiting neoplastic development can be rendered more active by suitable treatment, it is not possible to deny that oncolysis may be brought about, indirectly, by their hyperfunction.

In explanation of the lack of response shown by recurrent tumors to the various means of treatment, a possible acquired resistance of their cells has been proposed. But another reason for the difference in behavior between man and animals, or between spontaneous and implanted tumors, suggests itself. The animals used for experimental purposes are young and healthy, and their oncolytic defense is accordingly perfect. They therefore react to stimulation and defend themselves well, whereas in a human being, because of the physiological involution inseparable from age which characterizes the on-



cogenic period of his life, the organs are atrophic, so that the body is less able to respond to stimulation. The increase of this biological disadvantage with time, and with the exhausting demands of treatment, explains the unsatisfactory therapy of recurrences after a previous attempt to cure.

## SUMMARY

Certain fundamental principles of treatment may be derived from what has been said:

Importance must be attributed to suitable dosage, to the proportion between the mass to be destroyed and the curative agent, and to the alternation of oncolytic stimulation with various histogenic products. Finally histogenic treatment adds to its indirect action on antitlastic organs an important direct action by reason of the oncolytic substances introduced.

In developing the biological treatment of tumors, chemotherapy should be especially practised by means of autolysates, the importance of which has been emphasized by such authors as Vaughan, C. Lewin, Daels and Deleuze, Theilhaber, Lunckenbein, Koenigsfeld, Rohdenburg, Bullock, and Johnson, Briggs, Bristol, Bulkley, Little, Stammier, Mioni, Citelli, Bauer, Latzel, Wessely, and Klinger.

For the bibliography the writers quoted in my principal publications should be consulted; from these the present abstract has been made.

## REFERENCES

- FICHERA, G.: Policlinico, Sez. Prat., 1909, xvi, 1445.  
Arch. de Atti della Soc. Ital. di Chir., 1908, i, 437.  
Arch. de méd. expér. et d'anat. path., 1909, xxi, 617.  
Gazz. d. osp., 1910, i, 526.  
Tumori, 1911, i, 1.  
Policlinico, Sez. Chir., 1911, xviii, 121.  
Tumori, 1913, 2, 410.  
Ztschr. f. Krebsforsch., 1914, xiv, 46.  
Tumori, 1913, iii, 124.  
Tumori, 1914, iii, 760.  
Ztschr. f. Krebsforsch., 1914, xiv, 566.  
Tumori, 1914, iv, 191.